FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF AN ANTI MIGRAINE DRUG

A dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI - 600032.

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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Under the guidance of

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APRIL – 2015

JAYA COLLEGE OF PARAMEDICAL SCIENCE

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This is to certify that the dissertation entitled "**Formulation and Evaluation of Oral Disintegrating Tablets of an Anti Migraine drug"** Submitted by the candidate bearing Reg. No. 261211356 for The Tamil Nadu Dr. M.G.R. Medical University examinations.

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Date:
Place: Chennai

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(DR.N.NARAYANAN)

ACKNOWLEDGEMENT

I thank The Almighty for showering his blessings on me in completing my thesis

I express my sincere thanks to Chairman **Prof.A.Kanagaraj, M.A., M.Phil, Mrs.K.Vijayakumari M.A., B.Ed., S**ecretary**, Mr.Navaraj M.E,** Vice Chairman, Jaya College of Paramedical Sciences for providing me all the facilities in the college.

My sincere thanks to **Prof.A.Maheswaran, M.Pharm, (Ph.D), Principal**, College of Pharmacy, Jaya College of Paramedical Sciences, for providing me all the facilities in the college and also his constant encouragement throughout the course of project work.

I owe my gratitude and sincere thanks to my guide **Dr. N.Narayanan, M.Pharm. Ph.D.,** Director & HOD, Department of Pharmaceutics; Jaya College of Paramedical Sciences, for his unstained guidance and suggestions helped me for completing my project.

I owe my gratitude and sincere thanks to my Co-guide **Mr. Karthik, M.Pharm**, for his unstained guidance and suggestions helped me for completing my project.

I express my sincere thanks to **Mr. T. Munusamy Naidu,** Proprietor Restech Pharma, Puducherry , for giving me an opportunity to work and learn in their organisation .

I am deeply thankful to the Technical Assistant Mr. J. Haribabu, Jaya College of Paramedical Sciences, for his help him in completing this work.

I extend my special thanks to all other TEACHING STAFFS, who were whole hearted in every sense whom I have gained the moral support during the moments of occasional uncertainty.

With immense pleasure I record my hearty thanks all NON-TEACHING STAFF members for their valuable support during my project work.

I express my sincere thanks to all of our family members, friends and well wishers whose name I failed to mention but whose living memories, I have stored within my heart.

Last but not least I would like to thank my parents, family members for their continued support and inspiration

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I. INTRODUCTION

Solid oral drug delivery is the simplest and easiest way of administering drugs. Thesedosage forms have many advantages over other types of oral dosage forms. Therefore, most of the New Chemical Entities (NCE) under development are intended to be used as a solid dosage forms that originate an effective and reproducible in vivo plasma concentration after oral administration.

The aqueous solubility of a drug is one of the key physical properties that affect both its ADME profile and 'screenability' in High Throughput Screening (HTS).Solubility is the characteristic physicalproperty referring to 'the ability of a given substance, the solute, to dissolve in asolvent'. Enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Solubility and dissolution are the rate determining steps in drug absorption.

Table 1: Solubility Terms (According to USP)

Definition	**Parts of solvent required for one part of solute**
Very Soluble	<1
Freely Soluble	1-10
Soluble	10-30
Sparingly Soluble	30-100
Slightly Soluble	100-1000
Very Slightly Soluble	1000-10,000
Insoluble	> 10,000

Nearly 40 % of the drug molecules that have been discovered are lipophilic in nature.

Table 2: Biopharmaceutical Classification System (According to BCS classification by FDA)

Class	Description
Class I	Highly soluble, highly permeable
Class II	Poorly soluble, highly permeable
Class III	Highly soluble, Poorly permeable
Class IV	Poorly soluble, Poorly permeable

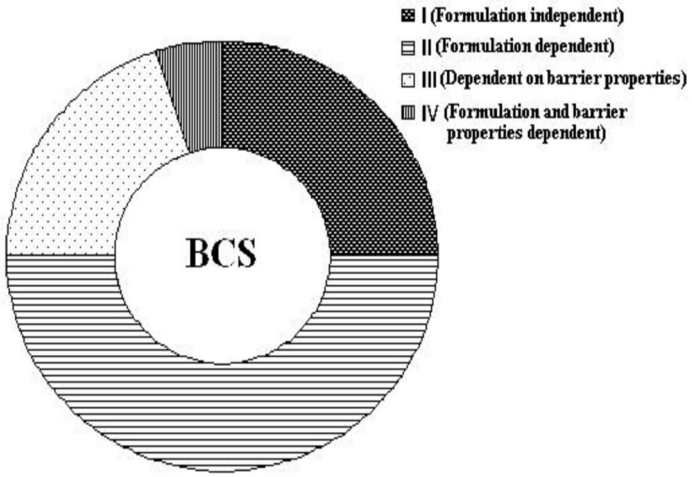


Figure 1: Graphical representation of Biopharmaceutical Classification System (Gaurav Tiwari et al., 2009)

1.1Dysphagia Fast Disintegrating Tablets (FDTs)

Dysphagia,[1-8] or difficulty in swallowing, is common among all age groups. Accordingto a study by Sastry et al., dysphagia is common in about 35% of the generalpopulation, as well as an additional 30–40% of elderly institutionalized patients and18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface,form, and taste of tablets. Geriatric and pediatric patients and traveling patientswho may not have ready access to water are most in need of easy swallowing dosageforms. Another study shows that an estimated 50% of the population suffers from this problem. These studies show an urgent need for a new dosage form that canimprove patient compliance.Solid dosage forms that can be dissolved or suspendedwith water in the mouth for easy swallowing are highly desirable for the pediatricand geriatric population, as well as other patients who prefer the convenience

ofreadily administered dosage forms.Although chewable tablets have been on themarket for some time, they are not the sameas the new ODTs.

Patients for whom chewingis difficult or painful can use these new tabletseasily. ODTs can be used easily in childrenwho have lost their primary teeth but do nothave full use of their permanent teeth**.** Recent market studies indicate that more thanhalf of the patient population prefers ODTs toother dosage formsand most consumerswould ask their doctors for ODTs (70%),purchase ODTs (70%), or prefer ODTs toregular tablets or liquids (>80%)**.**During the last decade, fast disintegrating tablet (FDT) technologies thatmake tablets disintegrate in the mouth without chewing and additional waterintake have drawn a great deal of attention.

The FDT is also known as *fast melting,fast dispersing, rapid dissolve, rapid melt,* and/or *quick disintegrating tablet.* AllFDTs approved by the Food and Drug Administration (FDA) are classified asorally disintegrating tablets. Recently, the European Pharmacopeia adopted theterm *orodispersible tablet* for a tablet that disperses or disintegrates in less than 3minutes in the mouth before swallowing. Such a tablet disintegrates into smallergranules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies fromseveral seconds to about a minute.

1.2Advantages of FDTs

- FDTs have all the advantages of solid dosage forms, such as good stability, accuratedosing, easy manufacturing, small packaging size, and easy handling by patients.
- FDTs also have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form.
- Theprimary patients for FDTs are pediatric, geriatric, and bedridden or developmentallydisabled patients; patients with persistent nausea; and patients who have little orno access to water.
- Application of FDTs can of course be extended to more generalpatients of daily medication regimens. From the pharmaceutical industry's point of view, FDTs can provide new dosage forms as a life cycle management tool for drugsnear the end of their patent life.
- Because the tablets disintegrate inside the mouth, drugs may be absorbed in thebuccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention andincreased bioavailability of drugs are possible.

- Because the pre-gastric drug absorption avoids the first-pass metabolism, the drug dose can be reduced if a significantamount of the drug is lost through the hepatic metabolism.

Disadvantages:

- Drugs that are absorbed at a specific site cannot be given in these dosage forms
- Requires special packaging as the tablets show high Friability which is expensive
- Suitable for low dose drugs

1.3. DESIRED CHARACTERISTICS AND DEVELOPMENT CHALLENGES OF FDTs: [1-3]

Because of administration of FDTs is different from administration of conventional tablets, the FDTs should maintain several unique properties, as listed below.

A. Fast Disintegration

FDTs should disintegrate in the mouth without additional water or with a verysmall amount (e.g., 1–2 mL) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquidsuspension, which can provide good mouth feel and smooth swallowing. The "fastdisintegration" usually means disintegration of tablets in less than 1 minute, but itis preferred to have disintegration as soon as possible.

B. Taste of Active Ingredients

Because of FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there shouldbe minimal or no residue in the mouth. A pleasant taste inside the mouth becomescritical for patient acceptance. Unless the drug is tasteless or does not have an undesirabletaste, taste-masking techniques should be used.

An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste-masking materials used in the dosage forms should be kept low **"AS LOW AS POSSIBLE"** to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should notbe broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the FDT formulations.

Physiology of Taste: [20, 29]

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue (Fig. 2). Bitter molecules bind to a G protein-coupled receptor type T2R on the apical membrane of the taste receptor cells (TRC) located in the taste buds. In humans, roughly 25 different T2R are described. Additionally, several alleles are known and about 100 different bitter phenotypes exist in man. TRC are specialized to a certain taste quality.

For the bitter modality, one TRC expresses more than one T2R type but not in all variants. On the other hand, it is now known that one particular bitter compound can bind to several T2R subtypes with distinct affinity and that at least some of the bitter receptor proteins, e.g., the hT2R47, are broadly tuned for several structural classes of bitter molecules. As a result, a bitter taste pattern for the cells occurs in a similar way to the olfaction process; however, the final signal to the brain is mainly "negative" or "bitter".

Following the binding of agonists to the T2R, phospholipase C is activated via a β-subunit of a G protein of the TRC which activates the IP3 (inositoltriphosphate) pathway in the cell. Calcium will be released from internal stores and at least the co-expressed ion channel TRPM5 will be activated and the cell depolarizes. In addition, the α-unit of the TRC-specific G protein gustducin may activate the PDE pathway of transduction.

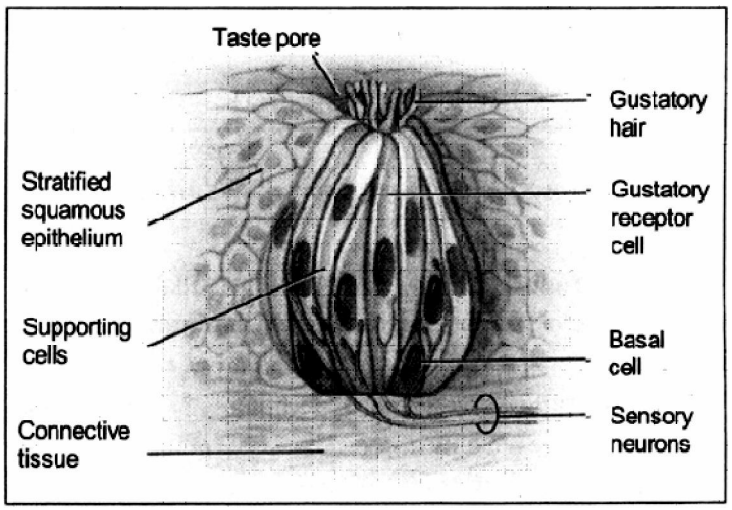


Fig. 2Structure of taste bud

C. Taste-masking techniques:[3-6]

The methods most commonly involved for achieving taste masking include various chemical and physical methods, which prevent the drug substance from interacting with taste buds. Various methods used for taste masking are:

-Addition of Flavouring and Sweetening agents

- Inclusion complexation
-microencapsulation
-Complexation with ion exchange resin
-Granulation
-Gel Formation
-multiple emulsion
-Bitterness Inhibitor
-prodrug approach

Taste masking with flavours, sweeteners, and amino acids:

It is known to most food technologists that bitter taste can be masked by strong flavours, especially by using so-called congruent flavours. These flavours cause a certain acceptance of bitterness due to their inherent occurrence.

Artificial sweeteners and flavours are generally being used along with other taste-masking techniques to improve the efficiency of these techniques. The unpleasant taste of certain formulations like mouthwashes and cough drops containing medicinal and bitter tasting substances such as eucalyptus oil can be masked by adding fenchone, borneol, or isoborneol. Cocoa or chocolate flavours preparations mask the bitterness of quinine (Becker et al. 1951), grapefruit flavours are widely used to mask pharmaceutical actives. In cola-type beverages, most consumers cannot detect the bitterness of caffeine due to the high dosage of sucrose, sweetener and acid. Another classical system is the suppression of bitterness by sodium salts. Sodium saltswhich are low in saltiness such as gluconate or acetate are the most successful maskers (Keast et al. 2005). A combination of sodium salts and L-arginine was used for the reduction of bitterness of certain peptides (Uchida et al. 2004).

Aspartame is used as a prominent sweetener in providing bitterness reduction. A very small concentration (0.8%) is effective in reducing the bitterness of 25% acetaminophen. Starch, lactose, and mannitol have also exhibited taste-masking properties of caffeine.

The mechanisms of the aforementioned bitter-masking technologies are not known. Probably, the masking activities are mostly caused by psychophysical effects due to the suppression of the off-taste by camouflage. Unfortunately, the use of strong flavours or tastants is not acceptable in a lot of applications. For example, it is not possible to use higher amounts of sodium salts in sweet beverages or sweeteners in savory applications. Therefore, the applicability of such compounds is only limited.

D. Drug Properties[15-16]

For the ideal FDT technology, the drug properties should not significantly affect thetablet property. Many drug properties could potentially affect the performance ofFDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity,compressibility, and bulk density of a drug can significantly affect the final tablet'scharacteristics, such as tablet strength and disintegration. The FDT technologyshould be versatile enough to accommodate unique properties of each drug .Several factors must be considered whenselecting drug candidates for delivery as ODTdosage forms. In general, an ODT isformulated as a bioequivalent line extension ofan existing oral dosage form. Under thiscircumstance, it is assumed that theabsorption of a drug molecule from the ODToccurs in the postgastric GIT segments,similar to the conventional oral dosage form.But this scenario may not always be the case.An ODT may have varying degrees ofpregastric absorption and thus, thepharmacokinetic profiles will vary.Therefore,the ODT will not be bioequivalent to theconventional oral dosage form. For example,ODT formulations of selegiline, apomorphine,and buspirone have significantly differentpharmacokinetic profiles compared with thesame dose administered in a conventionaldosage form. It is possible that these differences may, in part, be attributed to the drug molecule,formulation, or a combination of both. If significantly higher plasma levels have beenobserved, pregastric absorption leading to theavoidance of first-pass metabolism may playan important role. This situation may haveimplications for drug safety and efficacy,which may need to be addressed andassessed in a marketing application for anODT**.**

For example, safety profiles may beimproved for drugs that produce a significantamount of toxic metabolites mediated by firstpassliver metabolism and gastric metabolismand for drugs that have a substantial fractionof absorption in the oral cavity and segmentsof the pregastric GIT.Drugs having ability to diffuse and partitioninto the epithelium of the upper GIT (log P > 1,or preferable > 2); and those able to permeateoral mucosal tissue are considered ideal forODT formulations. Patients who concurrentlytake anticholinergic medications may not bethe best candidates for these drugs. Similarly,patients with Sjögren's syndrome or drynessof the mouth due to decreased salivaproduction may not be good candidates for these tablet formulation. Drugs which arevery bitter or otherwise unacceptable tastebecause taste masking cannot be achieved orthose which require controlled or sustainedrelease are unsuitable candidates of rapidlydissolving oral dosage forms.Researchers have formulated ODT for variouscategories of drugs used for therapy in whichrapid peak plasma

concentration is required toachieve the desired pharmacologicalresponse. These include neuroleptics,cardiovascular agents, analgesics, antiallergic,anti-epileptics.

E. Tablet Strength and Porosity

Because FDTs are designed to have a quick dissolution/disintegration time, thetablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into thetablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tabletstructure should also have a highly porous network. Because the strength of a tabletis related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption whilemaintaining high mechanical strength. In addition, low compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging inconventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragiletablets should be provided.

F. Moisture Sensitivity

FDTs should have low sensitivity to humidity. This problem can be especially challengingbecause many highly water-soluble excipients are used in formulation toenhance fast dissolving properties as well as to create good mouth feel. Those highlywater-soluble excipients are susceptible to moisture; some will even deliquesce athigh humidity. A good package design or other strategy should be created to protectFDTs from various environmental conditions.

G. Palatability

As most drugs are unpalatable, orallydisintegrating drug delivery systems usuallycontain the medicament in a taste-maskedform. Delivery systems disintegrate ordissolve in patient's oral cavity, thus releasingthe active ingredients which come in contactwith the taste buds; hence, taste-masking ofthe drugs becomes critical to patientcompliance.

H. Amount of drug

The application of technologies used for ODTsis limited by the amount of drug that can beincorporated into each unit dose. Forlyophilized dosage forms, the drug dose mustbe lower

than 400 mg for insoluble drugs andless than 60 mg for soluble drugs. Thisparameter is particularly challenging whenformulating a fast-dissolving oral films orwafers

I. Aqueous solubility

Water-soluble drugs pose various formulationchallenges because they form eutecticmixtures, which result in freezing-pointdepression and the formation of a glassy solidthat may collapse upon drying because of lossof supporting structure during the sublimation process. Such collapse sometimes can beprevented by using various matrix-formingexcipients such as mannitol than can inducecrystallinity and hence, impart rigidity to theamorphous composite

.

J. Size of tablet

The degree of ease when taking a tabletdepends on its size. It has been reported thatthe easiest size of tablet to swallow is 7-8 mmwhile the easiest size to handle was onelarger than 8 mm. Therefore, the tablet sizethat is both easy to take and easy to handle isdifficult to achieve.

1.4. Approaches to ODT Development[16-19]

The fast disintegrating property of the tablet isattributable to a quick ingress of water into the tablet matrix resulting in its rapiddisintegration. Hence, the basic approaches to develop rapidly dissolving oral dosage formsinclude maximizing the porous structure of thetablet matrix, incorporating the appropriatedisintegrating agent and using highly watersolubleexcipients in the formulation**.** As isoften the case, a technology that is originallydeveloped to address a particularadministration need can quickly become adopted as part of a pharmaceuticalcompany's product life cycle managementstrategy, which is precisely what hashappened with ODT technologies. Severalpatented technologies with their basis offormulation are listed in Table.The technologies that have been used byvarious researchers to prepare orallydisintegrating dosage forms include[4-6]:

1. Freeze-Drying or Lyophilization,
2. Molding,
3.Wet granulation followed by compression
4. DirectCompression,
5.Disintegrant addition,

6. Sublimation,
7. Spray Drying,
8. Mass Extrusion,
9. Cotton-candy process,
10. NanoCrystalTMTechnology,
11. Oral films/wafer

1.4.1Table3 ODT Patents [16-19]

Some ODT patents

Technology	Basis	Patent owner
Zydis	Lyophilization	R.P.Scherer Inc.
Quicksolv	Lyophilization	Janseen Pharmaceutica
Lyoc	Lyophilization	Farmlyoc
Flashtab	Multiparticulate Compressed Tablets	Ethypharm
Orasolv, Durasolv	Compressed Tablets	Cima Labs Inc.
RapiTab	Compressed Tablets	Schwarz Pharma
WOWTAB	Compressed Molded Tablets	Yamanouchi Pharma Technologies, Inc.
Fast melt	Molding	Élan Corp.
Ziplets	Molding	Eurand
FlashDose	Cotton-candy process	Fuisz Technology Ltd.

1.4.2 Table.4 ADVANTAGES AND DISADVANTAGES OF ODT TECHNOLOGIES16[-19]

Technique	Novelty	Advantage(s)	Disadvantage(s)
Zydis	First to market, Freeze dried	Quick dissolution, Self-preserving, increased bioavailability	Expensive process, poor stability at higher temperatures and humidities
Orasolv	Unique taste-masking, lightly compressed	Taste-masking is two-fold, quick dissolution	Low mechanical strength
Durasolv	Compressed dosage form, Proprietary taste masking.	Higher mechanical strength than Orasolv, good rigidity	Inappropriate with larger doses.
Flash Dose	Unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy.	High surface area for dissolution.	High temperature required to melt the matrix can limit he use of heat-sensitive drugs, sensitive to moisture and humidity.
Flashtab	Compressed dosage form containing drug as microcrystals.	Only conventional tableting technology is required.	--
Wowtab	Combination of low-mouldability and high-mouldabiity saccharides. SMOOTHMELT action gives superior mouth feel.	Adequate dissolution rate and hardness.	No significant change in bioavailability.
Oraquick	Uses patented taste-masking technology.	Faster and efficient production, appropriate for heat-sensitive drugs	--
Ziplet	Incorporation of water-insoluble inorganic excipients for excellent physical performance	Good mechanical strength, handling problems during manufacturing are avoided, satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg)	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution.

1.4.3Table.5. SOME OF THE MARKETED ODT FORMULATIONS

Brand name	Active ingredient	Application	Company	Technology
Claritin® RediTabs®	Loratadine	Antihistamine	Schering Corporation	Zydis®
Feldene Melt®	Piroxicam	NSAID	Pfizer	
Maxalt®-MLT®	Rizatritpan benzoate	Migrane	Merck	
Pepcid® ODT	Famotidine	Anti-ulcer	Merck	
Zyprexa®	Olanzapine	Psychotic disorders	Eli Lilly	
Zofran® ODT®	Ondansetron	Anti-emetic	Glaxo Smith Kline	
Risperdal® M-Tab™	Risperidone	Schizophrenia	Janssen	
Zubrin™(pet drug)	Tepoxalin	Canine NSAID	Schering Corporation	
Zelapar™	Selegiline	Parkinson's disease	Elan / Amarin Corporation	
Klonopin® Wafers	Clonazepam	Sedation	Roche	
Children's Dimetapp® ND	Loratadine	Allergy	Wyeth Consumer Healthcare	
Imodium Instant Melts	Loperamide HCl	Anti-diarrheal	Jannsen	
Propulsid® Quicksolv®	Cisapride monohydrate	Gastrointestinal prokinetic agent	Janssen	Quicksolv®
Tempra Quicklets Tempra FirsTabs	Acetaminophen	Analgesic	Bristol-Myers Squibb	OraSolv®
Remeron® SolTab®	Mirtazapine	Anti-depression	Organon Inc.	
Triaminic® Softchews®	Various combinations	Pediatric cold, cough and allergy	Novartis Consumer Health	

Zomig-ZMT® and Rapimelt®	Zolmitriptan	Anti-migraine	AstraZeneca	DuraSolv®
Alavert®	Loratadine	Allergy	Wyeth Consumer Healthcare	
NuLev®	Hyoscyamine sulfate	Anti-ulcer	Schwarz Pharma	
Kemstro™	Baclofen	Anti-spastic analgesic	Schwarz Pharma	
Benadryl® Fastmelt®	Diphenhydramine citrate	Allergy, sinus pressure relief	Pfizer	WOWTAB®
Nasea OD	Ramosetoron HCl	Anti-emetic	Yamanouchi	
Gaster D	Famotidine	Anti-ulcer	Yamanouchi	
Excedrin® QuickTabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb	QuickTabs™
Ralivia FlashDose®	Tramadol HCl	Analgesics	Biovail	FlashDose®
Zolpidem ODT	Zolpidem tartrate	Sleep disorders	Biovail	
Fluoxetine ODT	Fluoxetine	Anti-depression	Biovail	
Nurofen® Flashtab®	Ibuprofen	NSAID	Boots Healthcare	Flashtab®
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	Anti-ulcer	ETHEX Corporation	OraQuick
Cibalginadue FAST	Ibuprofen	NSAID	Novartis Consumer Health	Ziplets™

1.5. ADDITIVES USED IN ODT'S [32-35]

Various additives can be added to the formulation as long as they donot spoil the effects of present invention. They include

1. Disintegrating agents
2. Binding agents
3. Souring agents
4. Vesicants
5. Artificial sweeteners
6. Perfumes
7. Lubricants
8. coloring agents

1.5.1 DISINTEGRANTS USED IN FDTS:

Some patents use effervescent couples as their disintegrant, while others use a combinationofdisintegrants. Dobetti summarized different types of non-effervescentdisintegrants used in the pharmaceutical area.

• **Starch and modified starches.**This group includes natural starches (such as maize starch and potato starch), directly compressible starches (such as starch 1500), modified starches (such as carboxymethylstarches and sodium starch glycolate), and starch derivatives (such as amylose).

• **Cross-linked polyvinylpyrrolidone**

• **Modified celluloses** such as cross-linked sodium carboxymethylcellulose

• **Alginic acid and sodium alginate**

• **Microcrystalline cellulose**

• **Methacrylic acid-divinylbenzene copolymer salts**

1.5.2. Superdisintegrants: [19]

These are the agents added to tablet formulations to promote the breakup of tablet into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance.

Ideal characteristics:

- Should produce rapid disintegration
- Compactable enough to produce less friable tablets
- Effective at low concentration
- Have greater disintegrating efficiency

Mechanism of superdisintegrants:

There are four major mechanisms for tablets disintegration as follows:

1. ***Swelling:***

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

2. ***Porosity and capillary action (Wicking):***

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

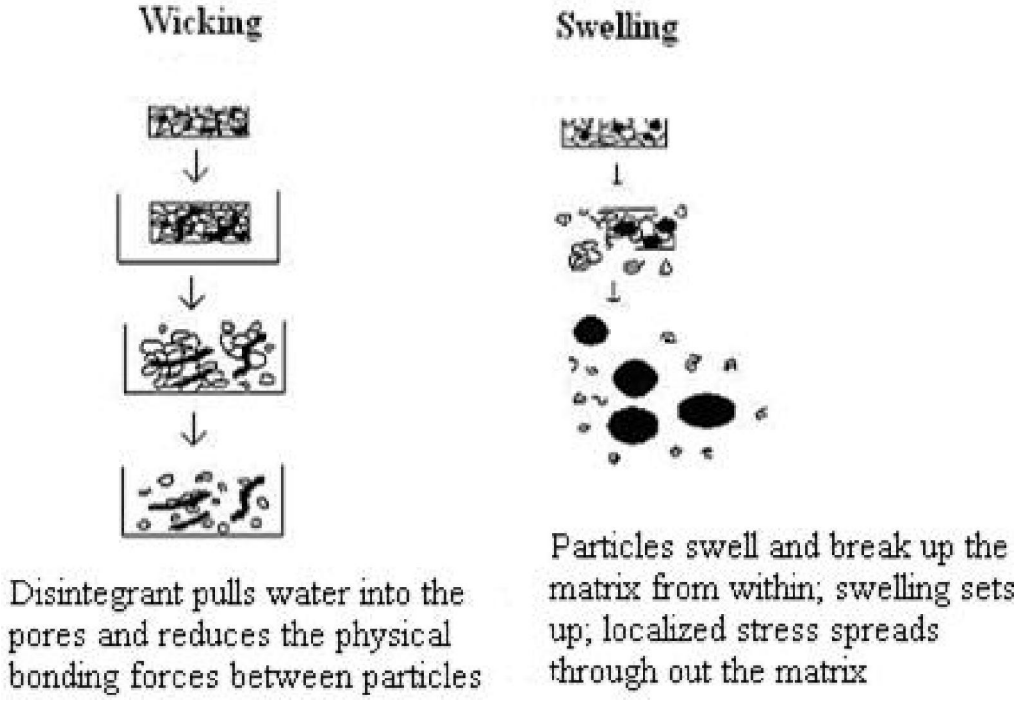


Figure.03 - Disintegration of Tablet by Wicking and Swelling (Pharmainfo.net)

3. *Due to disintegrating particle/particle repulsive forces*

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

4. *Due to deformation.*

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

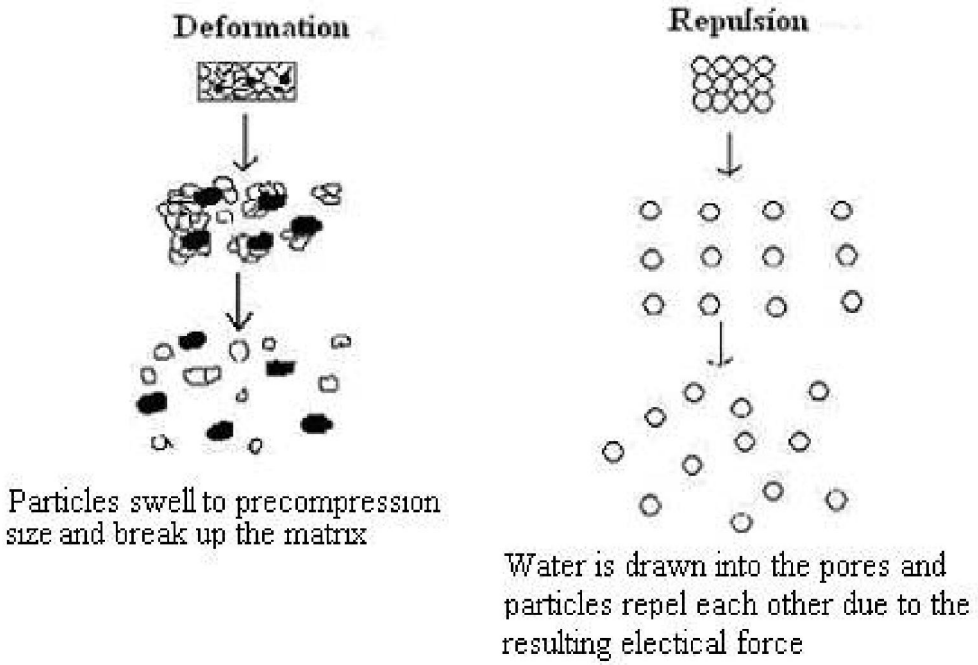


Figure 04 - Disintegration by Deformation and Repulsion (Pharmainfo.net)

1.5.2. Table 6 : Various superdisintegrants and their mechanism

Superdisintegrants	**Commercially available Grades**	**Mechanism of action**	**Special comment**
Crosslinked Cellulose	Crosscarmellose® Ac-Di-Sol®, Nymcel ZSX® Primellose®, Solutab®, Vivasol®, L-HPC.	Swells 4-8 folds in < 10 seconds. Swelling and wicking both.	Swells in two dimensions. Direct compression or Granulation Starch free.
Crosslinked PVP	Crosspovidon M® Kollidon® Polyplasdone®	Swells very little and returns to original size after compression but act by capillary action.	Water insoluble and spongy in nature so get porous tablet.
Crosslinked starch	Explotab® Primogel®	Swells 7-12 folds in < 30 seconds.	Swells in three dimensions and high level serve as sustain release matrix.
Crosslinkedalginic Acid	Alginic acidNF	Rapid swelling in aqueous medium or wicking action.	Promote disintegration in both dry or wet granulation.
Soy polysaccharides	Emcosoy®		Does not contain any starch or Sugar. Used in nutritional products.
Calcium silicate		Wicking action.	Highly porous, Light weight

1.5.3. Binding agents:

Powdered acacia, gelatin, pullulanetc

1.5.4. Souring agents:

Citric acid, tartaric acid, malic acid

1.5.5. Vesicants

Sodium bicarbonate

1.5.6. Artificial sweeteners

Saccharin sodium, glycyrrhizin, aspartame, stevia, thaumatin.

1.5.7. Perfumes

Lemon, lemon lime, orange, menthol

1.5.8. Lubricants

Magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc, sodiumstearylfumarate

1.5.9. Coloring agents

Food dyes, Food Lake dyes, red iron oxide

1.6 ODT Evaluation of Special Concern[17-19]

Crushing strength and friability can beassessed as stated in pharmacopoeias. Butsome tests are of special concern and theseinclude the following:

1.6.1 Wetting time

Wetting time of dosage form is related to thecontact angle. It needs to be assessed to give an insight into the disintegration properties ofthe tablets; a lower wetting time implies a quicker disintegration of the tablet. For thispurpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petridish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting ismeasured**.**

1.6.2 Disintegration test

The time for disintegration of ODTs isgenerally less than one minute and actualdisintegration time that patient can experienceranges from 5-30 seconds. The standard procedure of performing disintegration test forthese dosage forms has several limitationsand they are not suitable for the measurementof very short disintegration times. The methodneeds to be

modified for ODTs asdisintegration is required without water; thusthe test should mimic disintegration in salivarycontents. A modified dissolution apparatus isapplied to an ODT with a disintegration timethat is too fast to distinguish differences between tablets when the compendial methodis used. A basket sinker containing the tabletsis placed just below the water surface in acontainer with 900 mL of water at 37 ^{0}C, and apaddle rotating at 100 rpm is used. Thedisintegration time is determined when thetablet has completely disintegrated andpassed through the screen of the sinker**.**Various scientistshave developed new *invitro*methods that allow an accuratedetermination of disintegration test. Thedisintegration test is performed using a textureanalyzer instrument. In this test, a flat-endedcylindrical probe penetrates into thedisintegrating tablet immersed in water. As thetablet disintegrates, the instrument is set tomaintain a small force for a determined periodof time. The plots of some distance traveledby the probe generated with the instrument'ssoftware provide disintegration profile of thetablets as a function of time. The plot facilitates calculation of the start and end-pointof the tablet disintegration.

1.6.3 Dissolution test

The development of dissolution methods forODTs is comparable to the approach taken forConventional tablets, and is practicallyidentical. Dissolution conditions for drugslisted in a pharmacopoeia monograph, is agood place to start with scouting runs for abioequivalent ODT. Other media such as 0.1M HCl and buffer (pH 4.5 and 6.8) should beevaluated for ODT much in the same way astheir ordinary tablet counterparts.It has been suggested that USP 2 paddleapparatus is the most suitable and commonchoice for orally disintegrating tablets, with apaddle speed of 50 rpm commonly used.

1.6.4 Moisture uptake studies

Moisture uptake studies for ODT should beconducted to have an insight into the stabilityof the formulation, as several excipients usedare hygroscopic. Ten tablets from eachformulation are kept in a desiccator overcalcium chloride at 37^{0}C for 24 h. The tabletsare then weighed and exposed to 75% RH atroom temperature for two weeks. The requiredhumidity (75% RH) is achieved by keepingsaturated sodium chloride solution at thebottom of the desiccator for three days. Onetablet as control (without superdisintegrant) iskept to assess the moisture uptake due toother excipients. Tablets are weighed and thepercentage increase in weight is recorded

1.6.5. Fitness of Dispersion

This is a qualitative test specified by EP for ODTs.It is an assessment of the grittiness which arises due to disintegration of the tablet in to coarse particles.The test is performed by placing two tablets in 100ml water and stirring it gently,till the tablets get completely disintegrated.The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710 microns with out leaving any residue on the mesh.

1.7. Packaging of ODT

Packing is one of the important aspects in manufacturing ODT. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a good extent. The products obtained by lyophilization process including various technologies such hasZydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For these reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome-shaped blister, which prevents vertical movement of tablet with in the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv. WOW Tab, Pharmaburstoraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles.

1.8.Patient counseling in effective use of ODT[29]

ODT developed offers significant advantages for various group of patients, but the majority of patients receiving ODT have little understanding of this novel dosage form. Patients receiving ODT may be surprised when tablets begin to disintegrate/dissolve in mouth. As pharmacists are ideal persons to know about the recent technologies, thus have opportunity to educate the patients for effective treatment.

Counseling of patients about this dosage form can avoid any confusion and misunderstanding in taking ODT. Patient information that needs to be provided include:

- Storage of this dosage form as some of ODT developed may not have sufficient mechanical strength, which needs to be handled carefully.
- Patients with Siogren's syndrome or dryness of mouth or who take anticholinergic drugs may not be suitable candidates for administering ODT. Although no water is

required to allow drug to disperse quickly and efficiently but decreased volume of saliva may slow the rate of disintegration/dissolution and may reduce the bioavailability of the product.

- Patients need to be clearly told about the difference between effervescent and ODT. Some of technologies use effervescence, which experience a pleasing tingling effect on the tongue.
- Although chewable tablets are available in market and patient need to be counseled about differences between chewable and ODT tablets. This ODT can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently
- With the pharmacists counseling, intervention and assistance about ODT, all patients receiving this novel dosage form could be more properly and effectively treated with greater convenience.

II. LITERATURE REVIEW

- **GawandeShilpa et.al,2011.** was aimed towards the formulation and in vitro evaluation of orodispersibletablets by direct compression method using Risperidone as a model drug to enhance patientcompliance by masking the bitter taste of drug using cetyl alcohol in different ratios. Here crosspovidone andsodium starch glycolate in different concentrations (2%, 4%, 6% and 8%) are used assuperdisintegrant. All the batches were prepared by direct compression method andtablets were evaluated for weight variation, hardness, friability, in vitro disintegration time, invivo disintegration time, dispersion time, thickness, drug content and dissolution study. By considering disintegration time and concentration of superdisintegrant, formulation with drug to cetyl alcohol concentration (2:1) and crosspovidone 4% was optimised. Optimised tablet formulation was subjected to stability studies for three months at room temperature and 40c/75% RH.

- **Harshavardanguptha.K,et al.** FormulatedIt malate immediate release oral dosage forms, i.e., tablets and capsules, are most widely used drug delivery systemsavailable. These products are designed to disintegrate in the stomach followed by theirdissolution in the fluids of the GIT.Microcrystalline cellulose, Galen IQ and Dicalciumphosphate were used as directly compressible fillers. In order to obtain acceptableproduct several trials were conducted. Various pharmacopoeial evaluations of theformulations were conducted including weight variation, hardness, disintegration time,friability and *in-vitro* dissolution. Final selection of formulation was done based onpharmaceutical equivalence of development formulation to that of marketed one.Theimmediate release of the medicament is achieved by the inclusion of the super-disintegrating agents such as sodium starch glycolate, cross carmellose sodium, crosspovidone

- **Shaikh.Siraj et al,2011.** Formulated FDTs of Aceclofenac using different concentrations of superdisintegrants like sodiumstarchglycolate together with polyplasdoneXL10 prepared by wetgranulation technique followed by compression..Tabletswereevaluatedforweightvariation,Hardness,friability,Disintegrationtime,wettingtime,Dispersiontime.All formulations show iowweightvariation and

dispersion time less than90seconds.The optimized formulation showed good drug release profile at all timeintervals.It was concluded that improved aceclofenac dissolution was achieved with wet granulation technique.

- **Bhupendra G.Prajapati et al,2010.**prepared fast dissolving tablets of Domperidone by wet granulation using Sodium Starch Glycolate as super disintegrant and starch paste as a binder. The disintegrant incorporated during the wet granulation process as extragranular incorporation. $A3^2$full factorial design was applied to investigate the combined effect of 2 formulation variables:Superdisintegrants and starch paste. Here the concentration of Superdisintegrants and concentration of starch paste were taken as independent variables. The effect of Disintegration time, wetting time, Q_{30} and friability were taken as dependent parameters. The optimized batch obtained from the factorial design was compared withthe marketed products. The stability study of the optimized batch is also done at 40 C and 75%RH

- **Venkataramanareddy S et.al,2010.** Developed oral disintegrating tablets (ODT) ofinsoluble and low bitter drugs like zaleplon using tasteenhancers as a taste masking agents. ODT of zaleplon were prepared using different superdisintegrants by direct compression method. Mannitolwas used as a diluent and sodium lauryl sulphate was used as a wetting (surfactant) agent. Aspartame and Acesulfame Potassium were used forunpleasant taste masked from the zaleplon by cosifting and serial of blending with otherexcipients. The mixed final blend was then compressedinto tablets. The formulations were evaluated for weight variation, hardness, friability, wetting time, disintegrating time, dissolution, taste evolutionstudy and in vitro dissolution. All the formulation showed low weight variation with different disintegration time and rapid in vitro dissolution. Theresults revealed that the tablets containing taste enhancers had a good palatability for the patients.

- **Khan et al, 2007.** Have masked masked the intensely bitter taste of ondansetronHCl. Tastemasking was done by complexingondansetronHCl withaminoalkyl methacrylate copolymer (Eudragit EPO) indifferent ratios by the precipitation method. Drug-polymercomplexes (DPCs) were tested for drug content, in vitrotaste in simulated salivary fluid (SSF) of pH 6.2, and molecularproperty.The complex with drug-

polymer ratio of 8:2 did not show drug release in SSF; therefore, it was selected as an optimized ratio.

- **DebjitBhowmik**Telmisartan is an Anti-hypertensive drug which is insoluble in water, hence the drug may be slowly orincompletely dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore itsbioavailability is less (bioavailability 42%). He preparedFast Dissolving tablets of Telmisartan by using Superdisintegrants– Crosspovidone, Ac-de-sol, and sodiumstarch glycolate, level of addition to increase the rate of drug release from dosage form to increase thedissolution rate and hence its bioavailability. The tablets were prepared by Direct Compression methodsand the prepared blend and tablets were evaluated for their physicochemical properties and In-Vitrodissolution study. The evaluation study were performed such as Weight Variation, Thickness, Hardness,Disintegrating Time, Wetting Time, and In-Vitro Drug Release and Stability Study. The Disintegration timeof Fast Dissolving tablets were increased by the addition of concentration of Superdisintegrants.

- **D.M.Patel et al** Developed fast dissolving tablets of etoricoxib. Granules containing etoricoxib, menthol, crospovidone, aspartame and mannitol were prepared by wet granulation technique. Menthol was sublimed from the granules by exposing the granules to vacuum. The porous granules were then compressed in to tablets. Alternatively, tablets were first prepared and later exposed to vacuum. The tablets were evaluated for percentage friability and disintegration time. A 3^2 full factorial design was applied to investigate the combined effect of 2 formulation variables: amount of menthol and crospovidone. The results of multiple regression analysis indicated that for obtaining fast dissolving tablets; optimum amount of menthol and higher percentage of crospovidone should be used. Sublimation of menthol from tablets resulted in rapid disintegration as compared with the tablets prepared from granules that were exposed to vacuum. The optimized tablet formulation was compared with conventional marketed tablets for percentage drug dissolved in 30 min (Q_{30}) and dissolution efficiency after 30 min (DE_{30}). From the results, it was concluded that fast dissolving tablets with improved.

- **Mizumoto T et al., (1996);**Formulation design of a novel fastdisintegratingtablet.Intrabuccally dissolving compressed moldings comprising a

saccharide US 5576014 etoricoxib dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

- **Andries. F. Maris et al., (2003);** were studied the effect of compression force, humidity and disintegrant concentration on disintegration and dissolution of furosemide tablets.

- **Late SG et al.**, has done research on effect of disintegration promoting agent, lubricants and moisture treatment on optimized fast disintegration tablets

- **Chowhan ZT(1980**) has studied the effect of low and high humidity ageing on the hardness, disintegration time and dissolution rate of Dibasic calcium phosphate based tablets

- **Yourong Fu et al., (2004);** *Critical Reviews in* Orally Fast Disintegrating Tablet Developments, Technologies,Taste-Masking and Clinical Studies.

- **Jaysukh J Hirani et al., (2009);** Orally Disintegrating Tablets: A Review

- **Suresh Bandari et al.,** Orodispersible tablets- An overview

- **Mashru et al, 2008.** Used soliddispersion technique to mask the intensely bitter taste of artemether, an antimalerial drug and to improve its dissolution.Glycyrrhizin, which is also known as glycyrrhizinic (GLY) acid,is an oleanane-type triterpene glycoside which was used as a sweeteners was used to mask the bitter taste of drug in solid dispersion method.The solid dispersion of ARM and GLY in 1:0.5 and 1:1Mwas carried out using solvent evaporation method. Solid dispersion was characterized by solubility study, DSC, XRD and FTIR

III. NEED AND OBJECTIVE

Migraine[28-29] is a chronic neurological disorder characterized by moderate to severe headaches, and nausea. It is about three times more common in women than in men.The word derives from the Greekἡμικρανία (*hemikrania*), "pain on one side of the head",fromἡμι- (*hemi-*), "half", and κρανίον (*kranion*), "skull".The typical migraine headache is unilateral (affecting one half of the head) and pulsating in nature and lasting from two to 72 hours.Initial treatment is with analgesics for the headache, an antiemetic for the nausea, and the avoidance of triggers. The cause of migraine headache is unknown; the most supported theory is that it is related to hyperexcitability of the cerebral cortex and/or abnormal control of pain neurons in the trigeminal nucleus of the brainstem

3.1. Causes of Migraine Headache

The main cause of migraine headache is the enlargement of temporal artery found just under the skin of the temples. It causes nerves to stretch around the temporal artery that in turn triggers the release of chemicals causing inflammation, pain and even more dilation of the artery.

- Estrogen levels- Estrogen, mainly a female hormone, is also a cause of migraine headache. Therefore, more women than men experience migraines. Migraines caused to women due to estrogen occur just before, during, or after a menstrual period.
- Stress- Mental and physical tension, consistent overwork, sleep disorders or too little/too much sleep, fatigue, all can cause migraine headache.
- Caffeine- Excessive tea and coffee and even smoking and alcohol intake can cause migraine headaches.
- Birth control pills- It is self explanatory as to why they are one of the causes of migraines as they affect the estrogen levels in women.
- Nutritional deficiency- certain vitamins and other nutritional supplements are required to prevent inflammation and for proper working of muscles, veins etc. Not taking proper amount of nutrients or fasting for an extended period of time can thus cause migraine headache.
- Heredity- Many victims have a "migraine gene" that predisposes them to migraine attacks.

3.2. Symptoms of Migraine Headache

About 20% of migraine headache sufferers get visual warning before a migraine attack. They may see a kind of "aura" that may include flickering points of light, blind spots, or zig-zagging lines.

- Moderate to severe, throbbing headache- right side or left side of the head.
- Head pain that gets severe with increased physical activity.
- Sensitivity to light and/or sound.
- Nausea or vomiting.
- Red eyes with burning sensation in eyes
- Loss of appetite
- Migraine sufferer wants to stay all alone and finds comfort in silent and dark room
- Depression and irritability
- Numbness or weakness in an arm or leg .

In recent years, the importance of patient compliance,not only in drug efficacy but also in overall economicsof healthcare, has been increasingly recognized. Efforts toimprove patient compliance have included attempts toimprove the palatability of orally administered pharmaceuticalagents especially for children and elderly. Inparticular, a bitter taste is known to decrease patientcompliance, and thus reduce effective pharmacotherapy.Various techniques are used to mask the bitter taste of drug.

In the present work, model drug is a moderately bitter drug,an attempt has been made to mask the taste of modeldrug by using sweetners like aspartame and mannitol in the formulation.

The literature survey revealed that no work has been reported on ODT of the modeldrug

3.3. OBJECTIVE:

The main objective is to formulate ODT'S by using different superdisintegrants and sweetners in different ratio's and evaluating its characteristics in order to improve the release rate,disintegration time, tastemasking and also providing better patient compliance.

IV.PLAN OF WORK

4.1. Model drug and excipients profile

4.2. Procurement of drug, and excipients

4.3. Preformulation study

- Solubility studies
- Calibration curve of model drug
- ***Drug excipients interaction study***

  Differential scanning calorimetry
- Characterisation of API

4.4. Formulation of Tablets

- Selection of drug-excipients ratio
- Preparation of binder solution
- Wet granulation

Compression

Optimization of composition

a) Trial with different disintegrant
b) Trial with different concentration of excipients

Process optimization

Hardness challenge study

4.5. Evaluation of compressed tablets

Precompression parameters

Flow Properties (Angle of repose and Compressibility index)

Particle size distribution by dry sieve analysis

Postcompression parameters

- Weightvariation
- Hardness
- Thickness
- %Friability

- Disintegration time
- Wetting time
- Moisture uptake studies
- Fitness of dispersion
- Taste evaluation

4.6 . XRD Analysis of final formulation

4.7. FTIR study of final formulation

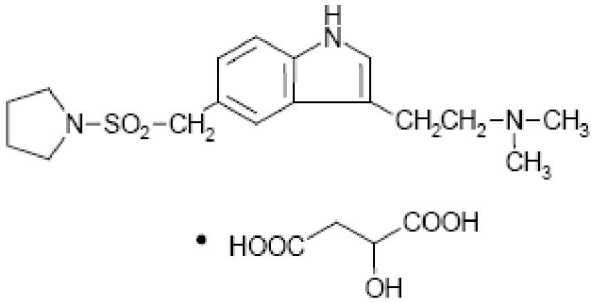
4.8. Stability study of optimized formulation

4.9. Invitro Drug Release studies

V.MODEL DRUG PROFILE [28-29]

Physicochemical parameters

Structure



IUPAC Name

1-[[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]sulfonyl]pyrrolidine (±)-hydroxybutanedioate.

Empiricalformula : $C_{17}H_{25}N_3O_2S$-$C_4H_6O_5$

Molecular Weight : 469.56

Category **:** Anti-migraine agent

Description **:**It is a white to slightly yellow crystalline powder

Melting point **:**167-173^{0}C

Solubility **:**Freely soluble in water and methanol but practically insoluble in ethanol and methylene chloride.

Mechanism of action

Modeldrugselectively binds with high affinity to 5–hydroxytryptaminergic receptors (5–HT $_{1D}$, 5–HT$_{1B}$ and 5–HT$_{1F}$). It has weak affinity for 5–HT$_{1A}$ and 5–HT$_7$ receptors, but has no significant affinity or pharmacological activity at 5–HT$_2$, 5–HT$_3$, 5–HT$_4$ or 5–HT-$_6$ receptors. It has been proposed that migraine symptoms are due to local cranial vasodilatation and/or to the release of pro-inflammatory and vasoactive neuropeptides from the trigeminal nerve endings. most likely acts on the 5–HT$_{1B/1D}$ receptors on the extracerebral, intracranial dilated blood vessels during a migraine attack, and on nerve terminals in the trigeminal system resulting in cranial vessel constriction, inhibition of neuropeptide release, and reduced transmission in trigeminal pain pathways

PHARMACOKINETICS

Absorption:

It is well absorbed after oral administration (absolute bioavailability about 70%). The rate and extent of absorption are not affected by administration with food.

Distribution:

The mean apparent volume of distribution is 180 to 200 liters

Protein binding:

Low (approximately 35%).

Biotransformation:

It is metabolized by one minor and two major pathways. Monoamine oxidase (MAO)-mediated oxidative deamination (approximately 27% of the dose), and cytochrome P450–mediated oxidation (approximately 12% of the dose) are the major routes of metabolism, while flavin monooxygenase is the minor route

Half-life:

3 to 4 hours.

Time to peak concentration:

Oral— 1 to 3 hours after administration

Elimination:

Renal; it is eliminated primarily by renal excretion (about 75% of the oral dose). Approximately 40% of an administered dose is excreted unchanged in uriine. Fecal; approximately 13% of the administered dose is excreted via feces, both unchanged and metabolized.

Usual adult dose

Oral, 6.25 or 12.5 mg (base) as a single dose. If necessary, an additional dose may be taken after two hours

Indications

Model drug is intended for the acute treatment of migraine with or without aura in adults.

Contraindications

It is contraindicated in patients with history,signs or symptoms of ischemic cardiac,cerebrovascular and peripheral vascular syndromes,valvular heart disease orcardiacarrythmias especially tachycardias.

Side effects

- mild headache (not a migraine).
- dry mouth, mild nausea.

- feeling of pain or tightness in your jaw, neck, or throat;
- pressure or heavy feeling in any part of your body.
- dizziness, drowsiness, weakness and
- mild tingly feeling.

DRUG INTERACTIONS

Ergot-Containing Drugs

These drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and it malate within 24 hours of each other should be avoided.

Monoamine Oxidase Inhibitors

Co administration of moclobemide resulted in a 27% decrease in it clearance and an increase in $C_{max}$of approximately 6%. No dose adjustment is necessary.

Propranolol

The pharmacokinetics of it were not affected by co administration of propranolol

Storage

Store at 25°C (77°F); excursions permitted between 15 and 30 °C (59 and 86 °F).

VI. EXCIPIENT PROFILE[25]

6.1.Mannitol

Structural Formula

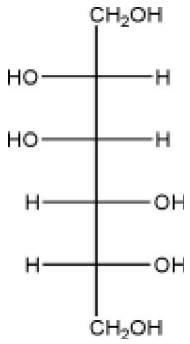


Table.7 Profile ofMannitol

Nonproprietary Names	• BP: Mannitol • JP: D-Mannitol • PhEur: Mannitolum • USP: Mannitol
Synonyms	Cordycepicacid,manna sugar; D-mannite; mannite; Mannogem,Pearlitol
Chemical Name and CAS Registry Number	D-Mannitol [69-65-8]
Empirical Formula	$C_6H_{14}O_6$
Molecular Weight	182.17
Functional Category	Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent, tonicity agent.
Description	occurs as a white, odorless, crystalline powder, or free-flowing granules. It has

	asweet taste, and imparts acooling sensation in the mouth.
Density	1.514 g/cm3
Melting point:	166–168°C
Solubility	
Stability and Storage	The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities Handling precautions	Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Mannitol may be irritant to the eyes; eye protection is recommended
Applications	Used as a diluent (10–90% w/w) in tablet formulations, Mannitol may be used in direct-compression tablet applications,for which the granular and spray-dried forms are available.

6.2. Aspartame

Structural Formula

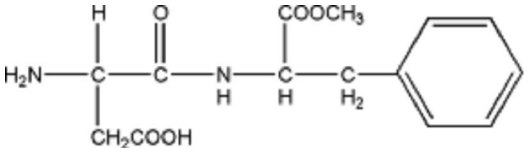


Table.8 Profile ofAspartame

Nonproprietary Names	• BP: Aspartame • PhEur: Aspartamum • USPNF: Aspartame
Synonyms	aspartyl phenylamine methyl ester; Canderel;Equal; methyl *N*-α-L-aspartyl-L-phenylalaninate; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; Tri-Sweet.
Chemical Name and CAS Registry Number	*N*-α-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]
Empirical Formula	$C_{14}H_{18}N_2O_5$
Molecular Weight	294.31
Functional Category .	Sweetening agent
Description	Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste
Density	1.347 g/cm3
Melting point	246–247°C

Solubility .	slightly soluble in ethanol (95%); sparingly soluble in water
Stability and Storage	The bulk material should be stored in a well-closed container, in a cool, dry place
Incompatibilities	aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate
Handling Precautions .	Measures should be taken to minimize the potential for dust explosion. Eyeprotection is recommended
Applications	Aspartame is used as an intense sweetening agent in beverage products, food products, andtable-top sweeteners. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

6.3. POLYPLASDONE XL -10

Table.9 Profile of Polyplasdone xl-10

Nonproprietary Names	• BP: Crospovidone • PhEur: Crospovidonum • USPNF: Crospovidone
Synonyms	Crospovidone, Polyvinylpyrrolidone.
Molecular weight	about 45,000 daltons
Description	Non-ionic, crosslinked, White, free flowing, compressible powder
pH(10 %slurry)	5.0 – 8.0
Composition	A synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone.
Functional categories	Disintegrant, Solubilizer
Solubility	Completely insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic. Swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure.
Melting point	Not available
Stability and storage conditions	Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Provide appropriate exhaust ventilation at places where dust is formed.Normal measures for preventive fire protection.
Incompatibilities	Strong oxidizing agents.
Applications	Super disintegrant and dissolution aid in wet granulation, dry granulation and direct compression.

6.4. Hydroxypropyl Cellulose(Klucel EXF)

Structural Formula

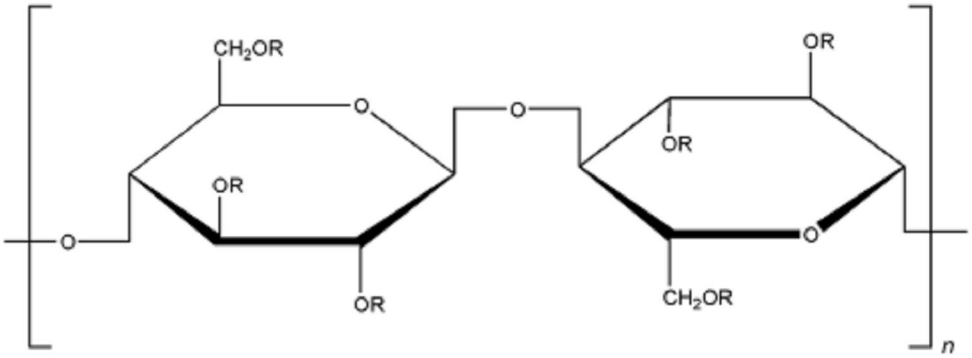


Table.10 Profile of Klucelexf

Nonproprietary Names	• BP: Hydroxypropylcellulose • JP: Hydroxypropylcellulose • PhEur: Hydroxypropylcellulosum • USPNF: Hydroxypropyl cellulose
Synonyms	Cellulose, 2-hydroxypropyl ether; oxypropylated cellulose.
Molecular weight	Variable
Description	White, free flowing, compressible powder
Viscosity	Lowest viscosity, varies based on the specific use
Composition	Nisso HPC consists of hydroxypropyl ethers obtained by the reaction of cellulose with propylene oxide.
Functional categories	It is used as a topical ophthalmic protectant and lubricant.
Solubility	Soluble in both water and organic solvents.

Melting point	Variable
Stability and storage conditions	Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Provide appropriate exhaust ventilation at places where dust is formed.Normal measures for preventive fire protection.
Incompatibilities	Strong oxidizing agents.
Applications	available for food use as a fat substitute, whipping aid, emulsion aid, and for film coating and tablet binding.

6.5. Cellulose, Microcrystalline

Structural Formula

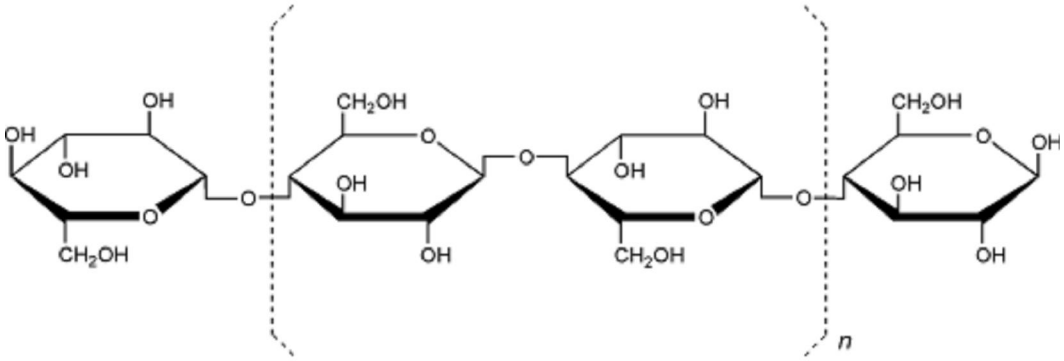


Table.11 Profile of Microcrystalline cellulose

Nonproprietary Names	• BP: Microcrystalline cellulose • JP: Microcrystalline cellulose • PhEur: Cellulosummicrocristallinum • USPNF: Microcrystalline cellulose
Synonyms	Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460;

	Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur
Chemical Name and CAS Registry Number Empirical Formula and Molecular Weight	Cellulose [9004-34-6.]
Functional Category	Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant
Description	Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as awhite, odorless, tasteless, crystalline powder composed of porous particles. It iscommercially available in different particle sizes and moisture grades that have differentproperties and applications.
Density	1.512–1.668 g/cm3
Melting point	260–270°C.
Solubility	slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents
Stability and Storage Conditions	Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place
Incompatibilities	Microcrystalline cellulose is incompatible with strong oxidizing agents
Handling Precautions	Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended
Applications	Microcrystalline cellulose is widely used in

	pharmaceuticals,primarily as a binder/diluent inoral tablet and capsule formulations where it is used in both wet-granulation and directcompression.

6.6. Sodium StearylFumarate

Structural formula

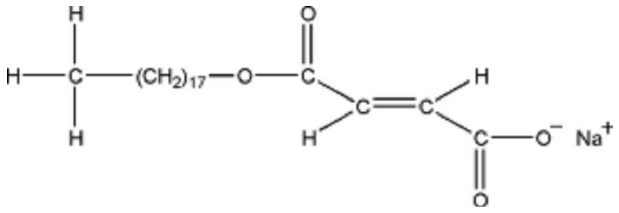


Table.12 Profile of Sodiumstearylfumarate

Nonproprietary Names	BP: Sodium stearyl fumarate PhEur: Natriistearylisfumaras USPNF: Sodium stearylfumarate
Synonyms	Fumaric acid, octadecylester,sodium mono stearyl fumarate
Chemical Name and CAS Registry Number	2-Butenedioic acid, monooctadecyl ester, sodium salt [4070-80-8]
Empirical Formula	$C_{22}H_{39}NaO_4$
Molecular weight	390.5
Functional Category	Tablet and capsule lubricant
Description	Sodium stearylfumarate is a fine, white

	powder with agglomerates of flat, circular-shaped particles
Density	1.107 g/cm3
Melting point	224–245°C
Solubility	Practically insoluble in acetone, chloroform,and slightly soluble in methanol.
Stability and Storage	The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Sodium stearylfumarate is reported to be incompatible with chlorhexidine acetate
Handling Precautions .	Sodium stearylfumarate should be handled in a well-ventilated environment; eye protection is recommended.
Applications	Sodium stearylfumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration. It is also used in certain food applications.

6.7.Sodium Starch Glycolate

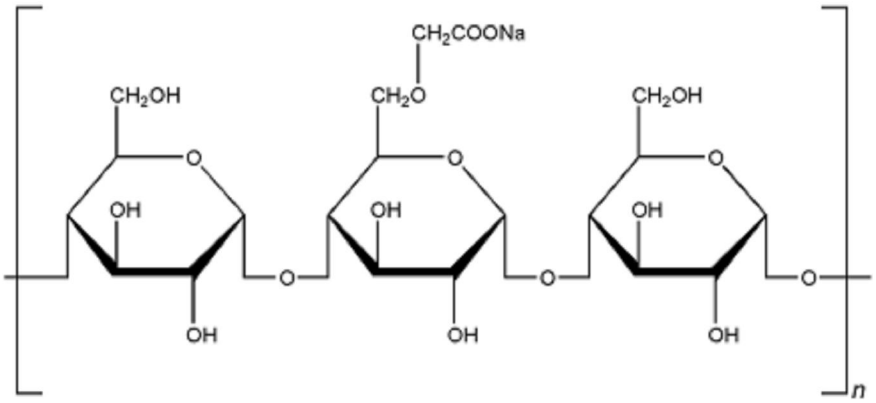


Table.13 Profile of Sodium starch glycolate

Nonproprietary Names	• BP: Sodium starch glycollate • PhEur: Carboxy methyl amylumnatricum • USPNF: Sodium starch glycolate
Synonyms	Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel, carboxymethyl ether, sodium salt; Tablo; Vivastar P.
Chemical Name and CAS Registry Number	Sodium carboxymethyl starch [9063-38-1]
Functional Category	Tablet and capsule disintegrant.
Description	Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder
Density (true):	1.443 g/cm3;
Melting point:	does not melt, but chars at approximately 200°C.
Solubility	sparingly soluble in ethanol (95%);

.	practically insoluble in water
Stability and Storage	Sodium starch glycolate is stable and should be stored in a well-closed container.
Incompatibilities	Sodium starch glycolate is incompatible with ascorbic acid
Handling Precautions	Sodium starch glycolate may be irritant to the eyes; eye protection and gloves are recommended.
Applications	as a disintegrant in capsule and tablet formulations.It is commonly used in tablets prepared by either direct compressionor wet-granulation processes.

6.8. Croscarmellose Sodium

Table.14 Profile of Croscarmellose sodium

Nonproprietary Names	BP: Croscarmellose sodium PhEur: Carmellosumnatricumconexum USPNF: Croscarmellose sodium
Synonyms .	Ac-Di-Sol; crosslinkedcarboxymethylcellulose sodium; *Explocel*; modified cellulose gum;Nymcel ZSX; *Pharmacel XL*; Primellose; Solutab; Vivasol
Chemical Name and CAS Registry Number	Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]
Molecular Weight	90 000–700 000.
Functional Category	Tablet and capsule disintegrant
Description	Croscarmellose sodium occurs as an odorless, white or grayish-white powder

Density	1.543 g/cm3
Solubility:	insoluble in water, although croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene
Stability and Storage	Croscarmellose sodium should be stored in a well-closed container in a cool, dry place
Incompatibilities	Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.
Handling Precautions .	Croscarmellose sodium may be irritant to the eyes; eye protection is recommended
Applications	Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules,tablets,and granules.

6.9. Colloidal Silicon Dioxide

Table.15 Profile of colloidalsilicon dioxide

Nonproprietary Names	BP: Colloidal anhydrous silica PhEur: Silica colloidalisanhydrica USPNF: Colloidal silicon dioxide
Synonyms	Aerosil; Cab-O-Sil; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed
Chemical Name and CAS Registry Number	Silica [7631-86-9]

Empirical Formula	SiO_2
Molecular Weight	60.08
Functional Category .	Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent
Description	It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.
Solubility	practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.
Stability and Storage	Colloidal silicon dioxide is hygroscopic. It should be stored in a well-closed container
Incompatibilities	Incompatible with diethylstilbestrol preparations
Handling Precautions	Eye protection and gloves are recommended For larger quantities, a dust respirator is recommended..
Applications	Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels

VII. MATERIALS

The following drug, excipients and chemicals were used for the formulation and evaluation of orodispersible tablets

.Table.16.List of chemicals and excipients

Sr.No	Excipient	Supplier
1	API	Mylan laboratories Ltd
2	Aspartame	The Nutra Sweet Company
3	Microcrystalline cellulose	Sri International
4	Polyplasdone xl-10	A.B.Enterprises
5	Sodium starch glycolate	Healthy life pharma pvt Ltd
6	Croscarmellose sodium	Alpha chemika
7	Kyron T-314	Corel pharma
8	Klucel EXF	Industrial chemicals pvt Ltd
9	Sodium stearylfumarate	BCM Corporation
10	Colloidal silicon dioxide	H.D.Pharmachem
11	Mannitol	Taj Pharma
12	Peppermint flavour	TriveniInterchempvt Ltd

VIII. EQUIPMENTS

Table.17. LIST OF EQUIPMENTS USED

S.No.	Name of the Equipment	Model	Supplier
1	Mechanical stirrer	RZR 2102 control	Heidolph
2.	Electronic weighing balance	BBA422-3SM	METTLER TOLEDO USA
3.	Disintegration Test apparatus	ED-2AL	ELECTROLAB
4.	Friabilator	EF/W	ELECTROLAB
5.	Laboratory oven	DTC-00R	NEWTRONIC
6.	Compression machine	CMD4	cadmach
7.	Stability chamber	-	thermolab scientific equipments
8.	Tablet hardness tester	Tablet tester 8M	pharmatron Dr. Schleuniger
9.	Induction cap sealear	CsP 300	Sigma CapSeal
10.	UV-Shimadzu	UV-2450	SHIMADZU
11.	Quadraco mill	197 S	GANSONS LTD
12.	Sieves	-	Retsch Solutions in Milling & Sieving
13.	DSC	822 e	METTLER TOLEDO
14.	XRD		BRUKER
15.	FTIR	Spectrum	PerkinElmer precisely.
16.	Dissolution apparatus	TDT-08L	ELECTROLAB

IX. PREFORMULATION STUDY

Drug Analysis

9.1.Solubility studies[26]

Solubility study of Model drug in different media:

Solubility studies were performed by taking required quantity of drug in 10 mL of different buffersat various pH conditions (pH 1.2, pH 4.5acetate, pH 6.8phosphate buffer, and water) separately up to its saturation and subjected to mechanical shaking at 100 rpm for 24 hrs. The resultant dispersions were collected and filtered through 0.2 µ filters and the concentration of drug was determined from absorbance at 227 nm.

9.2.Determination of λ_{max}

Procedure:

100mg of pure drug was taken and known concentration of drug solution was prepared by solubilizing in 0.1NHCL and it was scanned from 200-400 nm against the blank to fix absorption maxima. Spectrum of the model drug was obtained and $\lambda_{max}$of model drug was found to be 227 nm. Hence all further investigations were carried out at the same wavelength.

Calibration Curve of model drug in 0.1N HCl

10 mg of model drug was dissolved in 100 ml of 0.1N HCl (P^H1.2)to obtain the working standard of 100 µg/ml. Aliquots of 0.2ml to 0.7ml from the stock solution representing 2to7µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with 0.1N HCl. Absorbance of the above solutions was taken at λ_{max} 227nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 2 to 7µg/ml indicating its compliance with Beer's law.

Calibration curve of Model drug in Purified Water

Procedure: 10 mg of model drug was dissolved in 100 ml of distilled water to obtain the working standard of 100 µg/ml. Aliquots of 0.2 ml to 0.7 ml from the stock solution representing 2to7µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with purified water. The Absorbance of the above solutions was taken at λ_{max} 227 nm against the blank solution prepared in the same manner without adding the

drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 2 to7µg/ml indicating its compliance with Beer's law.

Calibration curve of Model drug in pH 6.8 Phosphate buffer

Procedure: 10 mg of model drug was dissolved in 100 ml of the pH 6.8 buffer to obtain the working standard of 100 µg/ml. Aliquots of 0.2 to 0.7ml from the stock solution representing 2to7µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with the pH 6.8 buffer.Absorbance of the above solutions was taken at λ_{max} 227 nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 2 to 7 µg/ml indicating its compliance with Beer's law

Calibration curve of Model drug in pH 4.5 acetate buffer

Procedure: 10 mg of model drug was dissolved in 100 ml of the pH 4.5 buffer to obtain the working standard of 100 µg/ml. Aliquots of 0.2 to 0.7ml from the stock solution representing 2to7µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with the pH 4.5 buffer.Absorbance of the above solutions was taken at λ_{max} 227 nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 2 to 7 µg/ml indicating its compliance with Beer's la

9.3. Drug and excipients interaction study

Differential Scanning Calorimetry

The possibility of any interaction between drug and excipients used in the formulation of tablets was assessed by carrying out the thermal analysis of drug, excipients and physical mixture of drug and excipients(Initial and stability charged).The thermal behavior of plain drug, excipients and physical mixturewere determined using differential scanning calorimeter at heating rate of 20°C /min. The measurements were performed at a heating range of 25 to 250^0C under nitrogen atmosphere.

9.4. X-Ray Diffraction study of model drug

Crystallinity of the drug was determined using the Bruker D8 Advance XRD with copper target. The conditions were: 40 Kv voltages; 40 mA current; at room temperature. The drug

was loaded on to the diffractometer and scanned over a range of 2θ values from 3^0 to 45^0 at a scan rate of 0.1^0 /sec.

9.5. Fourier Transform Infra Red spectrum of model drug

FTIR was performed by KBr pellet method. Drug and KBr were taken in 1:100 ratio and ground in mortar for even distribution of sample and KBr. Then it was prepared in the form of disk by applying pressure of 5 tons for 5 min using a hydraulic press and subjected to IR. The software used was spectrum (version 6.1.0) in the wave number range of 400-4000 cm^{-1}. The resolution is 4 cm^{-1}.

9.6. Characterisation of API

Particle size determination: Dry sieve analysis for particle size determination

Dry Sieving Method

An accurately weighed quantity of test specimen was placed on the top (coarsest) sieve, and lid was replaced. The nest of sieves was agitated for 5 minutes. Then each sieve was carefully removed from the nest without loss of material. Each sieve was reweighed, and the weight of material on each sieve was determined. The weight of material in the collecting pan was also determined in a similar manner. The nest of sieves were reassembled and agitated for 5 minutes. Each sieve was removed and weighed, as previously described. Upon completion of the analysis, the weights of material were reconciled. Total losses must not exceed 5% of the weight of the original test specimen.

Flow properties of API

Bulk density:

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (USP *Method I*).

Approximately 10gm of test sample, M was introduced into 25 mL dry measuring cylinder without compacting. The powder was leveled carefully without compacting and read the unsettled apparent volume V_0, to the nearest graduated unit. Bulk density was calculated, in g per ml, by the formula.

$$(M) / (V_o)$$

Generally replicate determinations are desirable for the determination of this property.

Tapped density:

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After measuring the initial weight and volume, the cylinder was mechanically tapped, and volume readings were taken until little further volume change is observed.

Procedure:

Cylinder containing the sample was tapped mechanically by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, the cylinder was tapped 500 times initially and the tapped volume was measured, V_a, to the nearest graduated unit. The tapping was repeatedfor an additional 750 times and the tapped volume was measured, V_b, to the nearest graduated unit.If the difference between the two volumes is less than 2%, V_b is the final tapped volume, V_f. It was repeated in increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. The tapped density was calculated, in g per mL, by the formula:

$$(M) / (V_f).$$

Generally replicate determinations are desirable for the determination of this property.

Compressibility Index:

The Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the *Compressibility Index* and the *Hausner Ratio.*

Compressibility Index— Calculate by the formula:

$$CI\ (\%) = \frac{V_o - V_f}{V_o} \times 100$$

Hausner Ratio— Calculate by the formula:

$$HR = \frac{V_f}{V_o}$$

Where V_0 - Bulk volume

V_f - Tapped volume

Table.18. Scale of Flowability (USP)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Determination of Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles.

Angle of repose was formed on a fixed base with a retaining lip to retain a layer of powder on the base. The base should be free of vibration. The height of the funnel was varied to carefully build up a symmetrical cone of powder. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately 2–4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone. If a symmetrical cone of powder cannot be successfully or reproducibly prepared, this method is not appropriate. Angle of repose was determined by measuring the height of the cone of powder and calculating the angle of repose, from the following equation:

$$\tan \alpha = h/r$$

Table.19. Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

X.METHODOLOGY

Formulation Development of ODT

10.1.Preparation of ODT using wet granulation technique

Orodispersible tablets were prepared by mixing API with intra granular excipients and then binder solution which was prepared by dissolving binder (klucelexf) in sufficient quantity of water was added. Then it was mixed well to form a damp mass. After that it was passed through 16 mesh to form granules.Then the granules were dried and the extra granular excipients were added and finally compressed to tablets.

10.2.Optimisation of composition

- **Trial with different disintegrants**

  Orodispersible tablets using wet granulation were prepared by taking different disintegrants like sodiumstarchglycolate, croscarmellose sodium,polyplasdoneXL-10and kyron T-314 and then disintegrant was optimized based on disintegration time.

- **Trial with different concentrations of excipients**

  ODT'S were prepared by taking different concentrations of excipients and then optimized.

10.3.Process optimization

Hardness challenge study

Orodispersible tablets were formulated at different hardness levels and then optimized.

10.4. FOMULATION DESIGN

Table.20.Optimization with different disintegrants

Ingredients	**F-1**	**F-2**	**F-3**	**F-4**
Intragranular	**Batch size**	**500**		
API	8.75	8.75	8.75	8.75
Avicel PH-101	20	20	20	20
Aspartame	8	8	8	8
Polyplasdone xl-10	**10**	**-**	**-**	**-**
Sodium starch glycolate	**-**	**10**	**-**	**-**

Croscarmellose sodium	**-**	**-**	**10**	**-**
Kyron T-314	**-**	**-**	**-**	**10**
Mannitol25C	53.25	53.25	53.25	53.25
Aerosil200	5	5	5	5
Klucel-EXF	3	3	3	3
Purified water	50	50	50	50
Extragranular	**Batch size**	**300**		
MannitolSD200	51	51	51	51
PolyplasdoneXL-10	**10**	**-**	**-**	**-**
Sodium starch glycolate	**-**	**10**	**-**	**-**
Croscarmellose sodium	**-**	**-**	**10**	**-**
Kyron T-314	**-**	**-**	**-**	**10**
AvicelPH-102	15	15	15	15
Aspartame	8	8	8	8
Peppermint flavour	1	1	1	1
Aerosil200	2	2	2	2
Sodium stearylfumarate	5	5	5	5
Totalweight **(**mg/tablet)	**200**	**200**	**200**	**200**

F1-Polyplasdonexl-10

F2-Sodiumstarchglycolate

F3-Croscarmellosesodium

F4-KyronT-314

Table.21.Optimisation with different concentrations of excipients

Ingredients	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**	**F-10**	**F-11**
Intragranular							
API	8.75	8.75	8.75	8.75	8.75	8.75	8.75
Avicel PH-101	20	20	20	20	20	20	**15**
Aspartame	**5**	-	8	8	8	8	8
Polyplasdone xl-10	10	**10**	**5**	**10**	**15**	**-**	10
Mannitol25C	56.25	61	58.25	53.25	48.25	63.25	58.25
Aerosil200	5	5	5	5	5	5	5
Klucel-EXF	3	3	3	3	3	3	3
Purified water	50	50	50	50	50	50	50
Extragranular							
MannitolSD200	54	59	56	51	46	61	56
PolyplasdoneXL-10	10	**10**	**5**	**10**	**15**	-	10
AvicelPH-102	15	15	15	15	15	15	**10**
Aspartame	**5**	-	8	8	8	8	8
Peppermint flavour	1	1	1	1	1	1	1
Aerosil200	2	2	2	2	2	2	2
Sodium stearylfumarate	5	5	5	5	5	5	5
Totalweight **(**mg/tablet**)**	200	200	200	200	200	200	200

Ingredients	**F-12**	**F-13**	**F-14**	**F-15**	**F-16**
Intragranular					
API	8.75	8.75	8.75	8.75	8.75
Avicel PH-101	**25**	-	20	20	20
Aspartame	8	8	8	8	8
Polyplasdone xl-10	10	10	10	-	10
Mannitol25C	48.25	73.25	46.25	56.25	53.25
Aerosil200	5	5	5	5	5
Klucel-EXF	3	3	**10**	-	3
Purified water	50	50	50	50	50
Extragranular					
MannitolSD200	46	66	51	51	48
PolyplasdoneXL-10	10	10	10	10	10
AvicelPH-102	**20**	-	15	15	15
Aspartame	8	8	8	8	8
Peppermint flavour	1	1	1	1	1
Aerosil200	2	2	2	2	2
Sodium stearylfumarate	5	5	5	5	**8**
Totalweight **(**mg/tablet)	200	200	200	200	200

Ingredients	**F-17**	**F-18**	**F-19**	**F-20**
Intragranular				
API	8.75	8.75	8.75	8.75
Avicel PH-101	20	20	20	20
Aspartame	8	8	8	8
Polyplasdone xl-10	10	10	10	**-**
Mannitol25C	53.25	53.25	53.25	58.25
Aerosil200	5	**5**	**5**	-
Klucel-EXF	3	3	3	-
Purified water	50	50	50	50
Extragranular				
MannitolSD200	56	50	53	51
PolyplasdoneXL-10	10	10	10	10
AvicelPH-102	20	-	15	15
Aspartame	8	8	8	8
Peppermint flavour	1	1	1	1
Aerosil200	2	**3**	-	**2**
Sodium stearylfumarate	-	5	5	5
Totalweight(mg/tablet**)**	200	200	200	200

XI. EVALUATION PARAMETERS OF ODT

11.1. Precompression parameters

Blend Characterization

Blend Characterizationparameters such as bulk density, tapped density, Compressibility Index, Hausner's ratio, Angle of Repose were performed and computed to 12 formulations of trial batches.

11.2.Postcompression parameters

All the batches of tablets were evaluated for various physical parameters like thickness, weight variation, friability, hardness, drug content and dissolution as per pharmacopoeial standards.[12]

A. Weight variation:

20 tablets were taken and weighed individuallyon a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Table.22.Acceptance criteria for tablet weight variation

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

B.Thickness:

Thickness of tablet is important for uniformity of tablet size. Thickness of tablets can vary with no change in weight because of the difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of the compression machine. Ten tablets were randomly selected and thickness was measured using vernier calipers and recorded

C.Crushing strength:

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Changes in hardness results in differences in disintegration and dissolution characteristics. The crushing strength of the tablet was determined using Schleuniger hardness tester.

D.Friability test:

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. For tablets weighing up to 650 mg each, take a sample consisting of the minimum number of tablets that makes a total mass of more than 6.5 gm. For tablets weighing more than 650 mg each take a sample of ten tablets. Dust should be carefully removed from the tablets prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, at 24-26 revolutions per minute and remove the tablets. Remove any loose dust from the tablets as before. If no tablets are cracked, split or broken, accurately weigh the tablets, and determine the friability (mass per cent of the lost mass with respect to the initial mass).

%Friability = (Loss in weight / Initial weight) x 100

E) Content uniformity test:

Ten tablets from each formulation were powdered. The powdered sample equivalent to 200 mg of drug was transferred to a volumetric flask and dissolved in required amount of 0.1NHCl suitably diluted with media and drug content was analyzedagainst blank by UV spectrophotometer at 227 nm. The percentage of drug present in the tablets was calculated.

F.Disintegration test

The time for disintegration of ODTs isgenerally less than one minute and actualdisintegration time that patient can experienceranges from 5-30 seconds. The standard procedure of performing disintegration test forthese dosage forms has several limitationsand they are not suitable for the measurementof very short disintegration times. The methodneeds to be modified for ODTs asdisintegration is required without water; thusthe test should mimic disintegration in salivarycontents. A modified dissolution apparatus isapplied to an ODT with a disintegration timethat is too fast to distinguish differences between tablets when the compendial methodis used. A basket sinker containing the tabletsis placed just below the

water surface in acontainer with 900 mL of water at 37 ^{0}C, and a paddle rotating at 100 rpm is used. Thedisintegration time is determined when thetablet has completely disintegrated and passed through the screen of the sinker

G.Wetting time

A study on wetting time reported the use of a piece of double folded tissue paper placed in a petridish containing 6ml of water.One tablet was placed on this paper and the time for complete wetting of the tablet was noted**.**

H.Moisture uptake study[17-18]

ODTs usually contain high concentration of hydrophilic excipients with the minimum possible hardness which together contributes to their increased susceptibility to moisture uptake. In order to maintain their physical integrity and surface texture, special attention is required during storage and packaging of these dosage forms. Therefore moisture uptake studies are recommended for ODTs.

The test can be carried out by keeping ten tablets along with calcium chloride in a dessicator maintained at 37C for 24hrs to ensure complete drying of the tablets. The tablets are then weighed and exposed to 75%RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the dessicator for 24hrs.The tablets were reweighed and the percentage increase in weight is recorded. If the moisture uptake is high it requires special dehumidified area for manufacturing and packing. The materials with high moisture resistant properties should be used for packaging e.g. alu strip pack, alu-alu blister or polyethylene sealing on blister.

I. Fitness of dispersion

This is a qualitative test specified by EP for dispersible tablets. It is an assessment of the grittiness which arises due to disintegration of the tablet into coarse particles. The test is performed by placing two tablets in 100ml of water and stirring it gently,till the tablets get completely disintegrated.The formulation is considered to form a smooth dispersion if the complete dispersion passes through a sieve screen with a nominal mesh aperture of 710µm without leaving any residue on the mesh.

Optimized formulation forms a smooth dispersion without leaving any residue on the mesh.

11.3 Taste evaluation

Taste evaluation wasdone in six healthy human volunteers by holding tablet in the mouth for 5 to 10 sec, then were asked to spit out; followed by rinsing the mouth by distilled water and the bitterness level was then recorded

XII.Accelerated Stability study of the optimized batch

In order to determine the change in evaluation parameters and in vitro release profile on storage, stability study of optimized batch was carried out at accelerated storage condition at temperature 40° ± 2° C and 75% ± 5% RH in a humidity chamber for 1 month. Sample were withdrawn after 30 days interval and evaluated for change in physical appearance

. XIII.In vitro dissolution studies: [12]

Dissolution study was conducted for formulations with different disintegrants using USP type-II apparatus (ELECTROLAB). The dissolution test was performed in buffers of different pH(0.1N HCl,6.8Phosphate buffer,4.5Acetate buffer, Water)50rpm and at a temperature of 37^0C±0.5^0C for 30 minutes. Ten milliliters of aliquots were periodically withdrawn at time intervals of 5, 10, 15, 20,and 30minutes. Then the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were diluted and analyzed spectrophotometrically at 227nm.

XII. REFERENCES

1. Yourong Fu Orally Fast Disintegrating Tablets: Developments, Technologies, Taste-Masking and Clinical Studies Purdue University, Departments of Pharmaceutics and Biomedical Engineering,

2. Jaysukh J hirani et al Oro dispersible tablets a review. Tropical Journal of Pharmaceutical Research, April 2009; 8 (2): 161-172

3. Ohta M, Hayakawa E, Ito K, Tokuno S, Morimoto K, Watanabe V. Intrabuccally rapidly disintegrating tablet. 1997. WO Patent 9,747,287.

4. Shimizu T, Morimoto S, Tabata T. Orally disintegrable tablets. 2001. US Patent 6,328,994.

5. Dobetti L. Fast-melting tablets: Developments and technologies. Pharm Tech, 2000; 12(9): 32-42.

6. www.drugbank.com

7. www.wikipedia.com